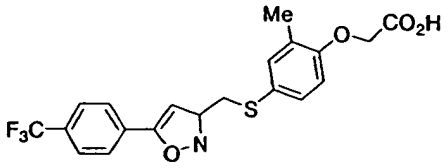
substituent at the 4-position of the isoxazole" (R^2 in our Claims) as the Examiner pointed out. Therefore, the Applicant described the EC_{50} value for PPARδ of the reference compound wherein R^2 is hydrogen is much higher than that of the compound of the claimed invention in the Applicant's Response filed on May 22, 2008. However, the Examiner in the last Office Action described that "a 4-fold difference is not considered to be a significant change as to indicate unexpected results."

The compound β-1-3 (Table 166 on page 265 of the instant specification) wherein R^2 is methyl shows an EC_{50} value of 9.9 nM, which is 4-times more potent than that of "Reference compound" (R^2=H, EC_{50}=37 nM). It was well-known that high in-vitro potency as well as in vivo drug disposition can cause a reduction of dose of a drug. Thus, β-1-3 has the potential to be a 4-times lower-dose drug compared to the reference compound. So, the 4-times EC_{50} increase of β-1-3 is very significant.

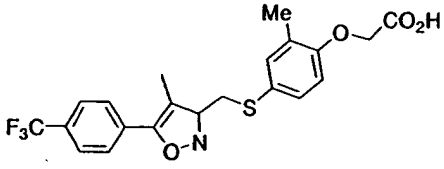
Additionally, the comparison data between a reference compound wherein R^2 is hydrogen and the compounds of the claimed invention are shown below.

The Applicant also synthesized β-1-15, Compound 1 and 2, which have CO_2Me, CH_2OMe and CH_2OEt groups at R^2 position (see Figure 1 below). Surprisingly, their EC_{50} values, which are 1.4 nM, 1.5 nM and less than 1 nM respectively, are more than 25 times lower than that of the reference compound. These results clearly indicate that a substituent at the R^2 position is needed to demonstrate very strong PPARδ activity. Such discovery of the present inventors is neither expected nor obvious from the prior art.

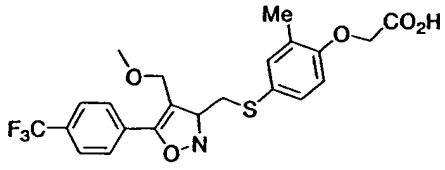
Figure 1.



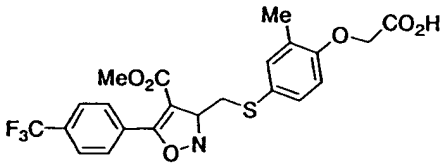
Reference compound EC50 = 37 nM



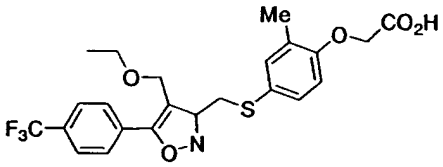
β-1-3 EC50 = 9.9 nM



β-1-15 EC50 = 1.5 nM



Compound 1 EC50 = 1.4 nM



Compound 2 EC50 < 1 nM

The foregoing experimental data is set forth in the Rule 132 Declaration of Dr. Matsumura attached hereto.

In view of the foregoing, it is respectfully submitted that the claimed invention is clearly unexpected and thus unobvious over the prior art. Accordingly, reconsideration and allowance is solicited.

Respectfully submitted,
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